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Light Dosimetry for Photodynamic Therapy in the Esophagus

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Background and Objective: **Photodynamic therapy (PDT) is an efficient technique to treat superficial early cancers in the pharynx, esophagus, and tracheo-bronchial tree. However, the lack of selectivity of some of the clinically used photosensitizers can result in significant damage to the healthy tissue during the treatment. In the esophagus, this may lead to medical complications such as stenosis and fistula. Insufficient selectivity may be compensated to some extent by accurate light dosimetry. Here, we present an approach to safer and more efficient PDT by improved light dosimetry in the esophagus.**
Study Design/Materials and Methods: **This includes the utilization of a suitable light distributor, the estimation of the radiant energy density in the tissue, and the knowledge of the esophagus morphology. The light distributor presently used in the clinic is described and several techniques to study light propagation in the esophageal wall have been investigated and are discussed. Thickness of different histological layers of the esophageal wall have been measured ex vivo and are presented.**
Results: **Under these conditions and based on a simple model of the light distribution in the tissue, some basic and clinically useful notions of light dosimetry can be drawn. These notions, associated with measured values of tissue optical properties at the wavelengths of interest with the presently used photosensitizers, are discussed regarding the particular morphology of the esophageal wall. In particular, the importance of the illumination wavelength from the safety point of view is shown.**
Conclusion: **The proposed approach allows for improved safety and efficacy of PDT in the esophagus, particularly in the clinical tests of new photosensitizers. Lasers Surg. Medicine 20:290–303, 1997.**

Key words: light penetration depth; PDT; photosensitizer; tissue optics

INTRODUCTION

In the upper aerodigestive tract, the tracheobronchial tree, and the esophagus, carcinogenesis is characterized by a tendency toward field cancerization leading to multicentricity of lesions [1]. During pretherapy broncho-esophagoscopy, carried out on ENT-cancer patients, the probability of detecting a synchronous second primary cancer can be as high as 20% [2]. In ~90% of the cases, these second primaries are detected at an early stage. In the esophagus, early carcinomas can be classified as either severe epithelial dysplasia, in situ carcinoma, or micro-invasive carcinoma, as illustrated in Figure 1.

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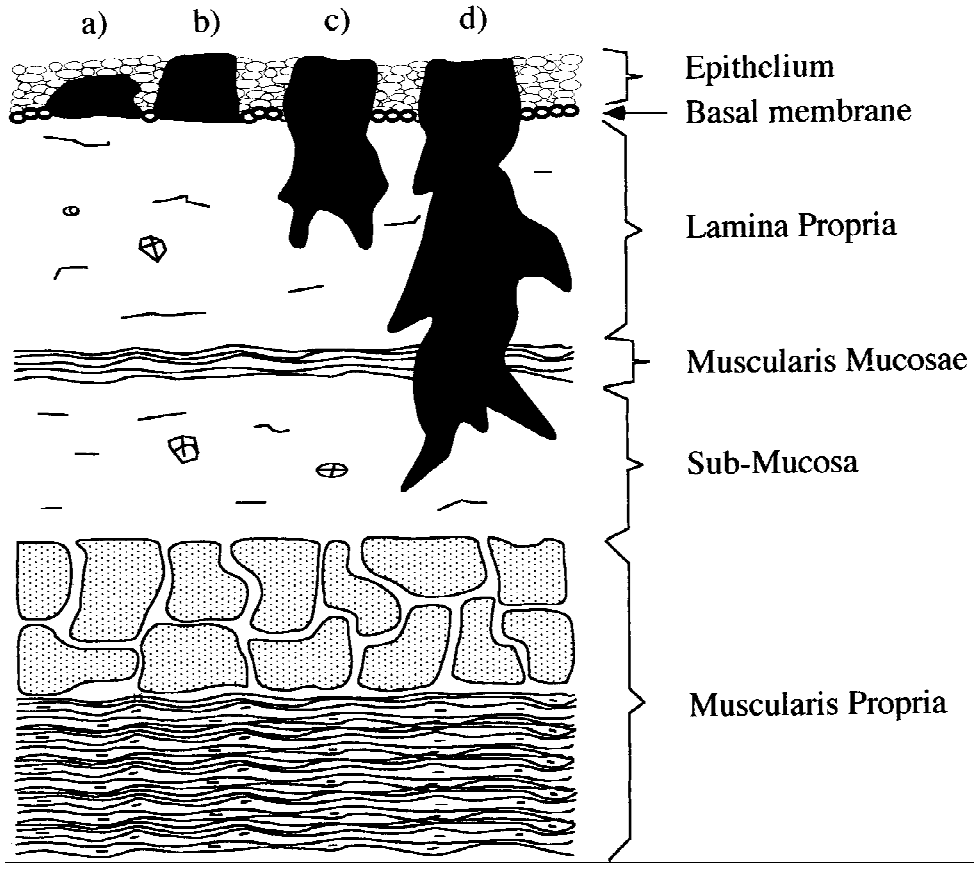

Fig. 1. Schematic diagram of tissue layers of the esophagus wall [3]. Definitions of different carcinoma stagings: (**a**) dysplasia; (**b**) in situ carcinoma, it does not penetrate the basal membrane and is not vascularized; (**c**) micro-invasive carcinoma perforates the basal membrane but does not invade deeper than the muscularis mucosa; (**d**) invasive carcinoma invades the submucosa.

In the oral cavity, the excision of early squamous cell carcinomas, e.g., by means of a CO_2 laser is an efficient procedure, leaving no functional sequelae [4]. In the pharynx, and to an even larger extent in the esophagus as well as in the tracheo-bronchial tree, the treatment of such lesions may give rise to insoluble problems. Conventional treatment modalities (chemotherapy, surgery, and radiotherapy), applied individually or combined to the primary and second primary tumors, lead to a high rate of morbidity and mortality in these patients, often due to their poor general condition. Photodynamic therapy [5–9] (PDT) can be a more efficient and less aggressive treatment for these kinds of superficial cancers in the pharynx, esophagus, and tracheo-bronchial tree. This therapy is based on the selective localization of a dye in some neoplastic tissues as compared to the surrounding healthy tissue. Phototoxic properties of the dye allow the selective destruction of tumors by irradiation of the site at the appropriate wavelength.

At the present time, clinically used photosensitizers in PDT have one or both of the two main drawbacks, i.e., skin photosensitization and insufficient selectivity. Skin photosensitization (sunburn) generally can be avoided. The lack of selectivity, i.e., an insufficient ratio between photosensitizer concentration in tumoral tissue and in healthy surrounding tissue, may result in significant damage to the healthy tissue during the photodynamic treatment of the tumor. Since the therapeutic effect is, among other factors, determined by the radiant energy density [J/cm^3] absorbed by the photosensitizer and also by the spatial distribution of the radiant energy fluence rate [W/cm^2] in the tissue, insufficient selectivity may be compensated to some extent by accurate light dosimetry. Inaccurate light dosimetry can lead to incomplete treatment of the tumor re-

sulting in recurrence. It can also lead to complete necrosis of the tumor as well as significant damage to the healthy tissue surrounding the treated site. In the latter case, this may lead to medical complications, e.g., fistula and stenosis in the esophagus. Hence, with most of the photosensitizers currently undergoing clinical testing, accurate light dosimetry is of primary importance. In future sensitizers, a combination of selectivity, accurate sensitizer dosing, and adjusted photobleaching rate may render accurate light dosimetry less essential [10,11].

At the present stage of clinical PDT development, light dosimetry is a complex problem for the clinician. The radiant energy fluence rate distribution in the tissue is difficult to estimate accurately. Models are numerous and associated with well-defined experimental conditions, rarely observed in a clinical context. The specific optical parameters are difficult to measure in situ. Furthermore, other treatment parameters may not yet be optimized. New photosensitizers with improved selectivity and shorter and/or reduced cutaneous photosensitization are being investigated. The optimal utilization conditions and the characteristics of these new photosensitizers, such as injected dose, optimal treatment time, selectivity, excitation wavelength, photobleaching rate, and toxicity, must be determined. Therefore, some degree of clinical optimization remains essential, at least until a representative animal model is found. Clinical experimentation includes tumor treatment as well as tests on normal tissue [12]. Such an approach implies an optimized number of experiments with minimal risk of medical complications. Future routine PDT in the clinic will require conditions to ensure safety and therapeutic effectiveness in spite of interpatient variability, different tumor locations, and staging.

In this report, our approach to solve the dosimetry problem at the present stage of the clinical PDT development is presented. As the morphology of the organ to be treated is an important parameter in our case, the structure of the esophageal wall is presented. In particular, its thickness and the thickness of its different histological layers have been measured ex vivo under several conditions (at rest and under the conditions occurring during PDT). A safe and effective dosimetry implies a well-controlled light illumination of the tissue. This is obtained by using a specially designed light distributor. The prototype presently used in clinic is described. Several techniques to study and to describe light propagation in the esophageal wall have been investigated and are discussed here. Finally, we show that numerous dosimetry questions can be solved and the safety of PDT in the esophagus can be improved by simple calculations based on a simple model of light propagation. The presented calculations have been done for two wavelengths of interest with the presently used photosensitizers, i.e., 514 and 630 nm. They demonstrate the importance of the illumination wavelength, in particular, regarding the safety of PDT in the esophagus.

MATERIALS AND METHODS

Esophageal Wall

The spatial distribution of the radiant energy fluence rate in tissue is determined by the light distributor and by the geometry and the optical properties of the site to be treated. In our present application, the latter is the esophagus, i.e., a tubular organ. At rest, its mucous membrane exhibits many deep folds and the wall thickness is typically 3.5 mm for an adult human being (see Fig. 2). The wall is composed of six principal layers (Fig. 1). The first layer is a squamous stratified epithelium ~200 μm thick. The epithelium is separated from the rest of the esophagus wall by the basal membrane. Below the basal membrane lies a first layer of loose connective tissue rich in blood and lymph vessels, the lamina propria, ~0.5 mm thick. Then follows a thin muscular layer, the muscularis mucosae. The second layer of connective tissue, the submucosa, is ~0.75 mm thick. It is well vascularized and relatively loose, allowing strong distension. Finally, the esophagus is covered by the muscularis propria, a membrane of ~2 mm thick, composed of two layers of muscle. In the internal sublayer, i.e., close to the lumen, the muscle cell orientation is generally circular; in the external sublayer, it is mostly longitudinal.

Light Distributor

In light dosimetry, one source of error can be a misunderstanding of the radiometric quantities used to characterize the light distributor and to describe the light propagation in the tissue. For convenience, some definitions of radiometric quantities are summarized below (International Standard ISO 31/6 1980) [13]. The radiant power or radiant energy flux [W] is the power emitted, transferred, or received as radiation. The radiant energy [J] is the energy emitted, transferred, or received as radiation. The radiant energy density

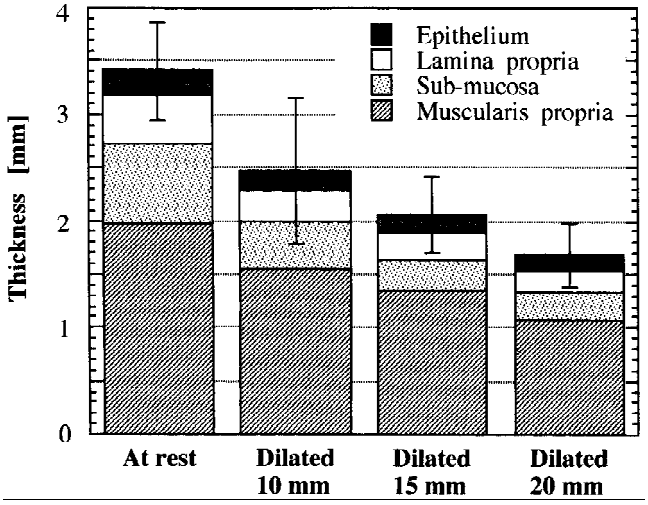

Fig. 2. Ex vivo measurements of the thicknesses of different tissue layers of the esophagus with the wall undilated and dilated by cylindrical light distributors of different diameters [21]; see Figure 4. The latter three measurements have been made with cylindrical light distributor diameters of, respectively 10, 15, and 20 mm. These light distributors have been inserted in resected esophagus and, before fixation in formol solution, the esophagus has been extended to the length measured before the resection. These measurements have been performed on 14 autopsy species.

[J/m^3] is the radiant energy in an element of volume, divided by that element. The radiant energy fluence rate [W/m^2] is, at a given point in space, the radiant energy flux incident on a small sphere, divided by the cross-sectional area of that sphere. The irradiance [W/m^2] is, at a point of the surface, the radiant energy flux incident on an element of the surface, divided by the area of that element. Radiant energy fluence rate and irradiance, even if described by the same units, must not be confused. Usually, radiant energy fluence rate is used to describe the light in the tissue since this quantity is related in a straightforward way to the radiant energy absorbed in the tissue, particularly by the sensitizer. From an experimental point of view, the radiant energy fluence rate is measured by using an isotropic optical probe [14–20], i.e., a detector with an omnidirectional sensitivity to the light. Irradiance is preferentially used to describe the light transferred at the boundaries, e.g., at the tissue surface or at the surface of the light distributor. In a highly diffusing medium such as biological tissue at the wavelengths of interest in PDT, the radiant energy fluence rate is frequently estimated from the irradiance at the tissue surface. The latter can be measured by a flat detector.

To illustrate the above notions, we consider some simple experimental examples. The hypothetical medium is now assumed to be absorbing with refractive index matching boundary conditions in order to simplify the model by neglecting all reflections. In the first example, Figure 3(a), the light source provides an infinitely wide collimated and perpendicular beam illuminating a black nonreflecting surface. The irradiance measured with the flat detector with one light sensitive surface facing the light source, and the radiant energy fluence rate determined with the isotropic detector are equal to the irradiance at the source surface. In the next example, Figure 3(b), the illuminated black surface is tilted relative to the incident collimated beam. The radiant energy fluence rate measurement is not modified by the inclination of the medium whereas the irradiance at the medium surface decreases ($I = Io \cos\theta$). The last example is illustrated in Figure 3(c). The light source is a infinitely wide plane surface emitting diffuse light with a Lambertian angular distribution. The illuminated black surface is parallel to the light source surface. The irradiance at the tissue surface is equal to the irradiance at the source surface. The radiant energy fluence rate is two times the irradiance of the light source. It clearly appears from these three examples that the irradiance, which is the quantity of reference in light dosimetry, must be carefully measured with a suitable probe.

To obtain a homogeneous and well-controlled light distribution over the entire surface to be irradiated in PDT of the esophagus (this is a primary condition for having a controlled light dosimetry), a cylindrical light distributor [21,22] (see Fig. 4) has been developed with different diameters, generally of the order of 15–20 mm. Such diameters are suited to distend and to smooth the esophagus wall surface. This light source, in contact with a diffusing medium such as living tissue, supplies a uniform light distribution to the surface of the organ. The light distributor induces a dilatation of the esophageal wall which consequently decreases in thickness to 1.5–2 mm (Fig. 2). This change in thickness has to be carefully considered in PDT of the esophagus from a geometrical point of view (tissue thickness to be treated) as well as from the optical point of view (change of the tissue optical properties). At present, we restrict most of our treatment by PDT to early carcinomas at most in their microinvasive stage (Fig. 1), hence, with depths of < 1 mm [3,7,21]. The optical dosimetry deter-

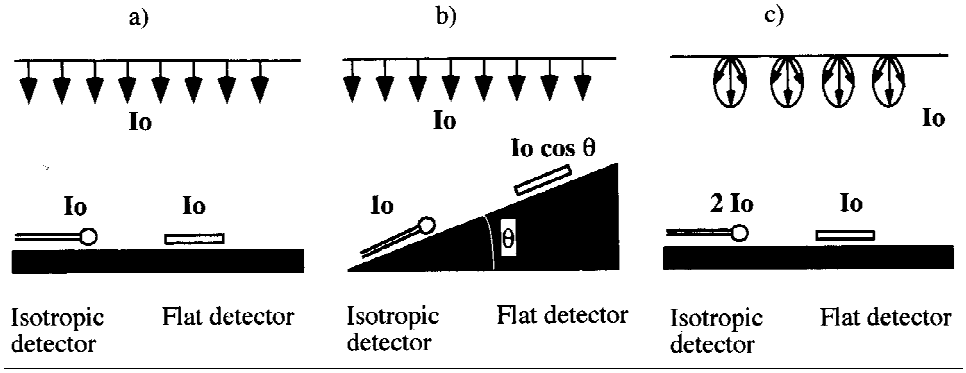

Fig. 3. Irradiance and radiant energy fluence rate measurement in three different experimental conditions.

mines the irradiance [W/m^2] applied by the light distributor and suitable to treat a tumor $\leq$ 1 mm thick without the risk of perforating the 1.5–2 mm thick esophageal wall. Until recently, when we found conditions for therapy with the dye mesotetrahydroxyphenylchlorin (mTHPC), which yielded selective necrosis [12], the irradiances necessary for curative PDT at the applied conditions also induced necrosis of the healthy tissue surrounding the tumor. A circular irradiation of the esophageal wall may even (and has occasionally) lead to stenosis. Complete stenosis can be avoided by reducing the surface irradiated. Hence light distributors with somewhat reduced circular irradiance geometries, e.g., 240°, have been designed and clinically used (Fig. 4).

Light Distribution in Tissue

To evaluate the radiant energy fluence rate [W/m^2] distribution in biological tissue, two main approaches previously have been investigated. The first method consists of measuring this distribution by inserting an optical microprobe with an isotropic response [14–20] in the tissue. The position of the microprobe in the tissue must be known accurately and the microprobe should not significantly perturb the light distribution in the tissues. In our experiments we use an isotropic probe based on the fluorescence of a ruby sphere glued to the end of an optical fiber [14,15]. The principle of this probe is that the fluorescence of the ruby sphere can be excited by visible light (between 350 and 650 nm) at the wavelengths of interest coming from nearly all directions in space. Upon excitation, ruby fluoresces efficiently near 693 nm. Thus this probe measures a value that is proportional to the true radiant energy fluence rate. The diameter of the ruby sphere is 200 μm. Typical angular responses are shown in Figure 5. By using a ruby sphere, a change of the isotropy and the sensitivity due to the photobleaching of the fluorescent tip cannot occur. Moreover, the ruby fluorescence decay time is in the order of several milliseconds depending on the Cr^{3+} concentration. Thus the ruby fluorescence and the tissue autofluorescence at 693 nm with its decay time in the order of 10 ns can be easily differentiated e.g., by a lock-in technique [15].

Performed in vivo, such a measurement may be used to determine the radiant energy fluence rate only under certain quite restricted conditions [14]. In the esophagus, it does not appear reasonable to attempt such a procedure. Ex vivo measurements with a resected esophagus have been performed, but several artifacts are induced in this way. Changes, particularly in the optical properties of the tissue, are due not only to the change in vascularization [5] or in water content, but also are a consequence of the variations of mechanical properties (elasticity) of the esophageal wall. Both in vivo and ex vivo, the conditions for such measurements are not always easily accessible in our surroundings, so only limited data are available and the variance from one patient to another is difficult to ascertain. Moreover, an accurate radiant energy fluence rate measurement is hard to achieve in soft tissue, especially close to the light source, even with a very small optical probe as several problems may occur. First, when the probe displacement is toward the light source, the tissue is compressed, as illustrated in Figure 6a. If the probe is moved away from the light source, a tissue distension and a local detachment of the tissue from the light source surface (Fig. 6b), or a structural alteration of the tissue close to the surface, e.g., mainte-

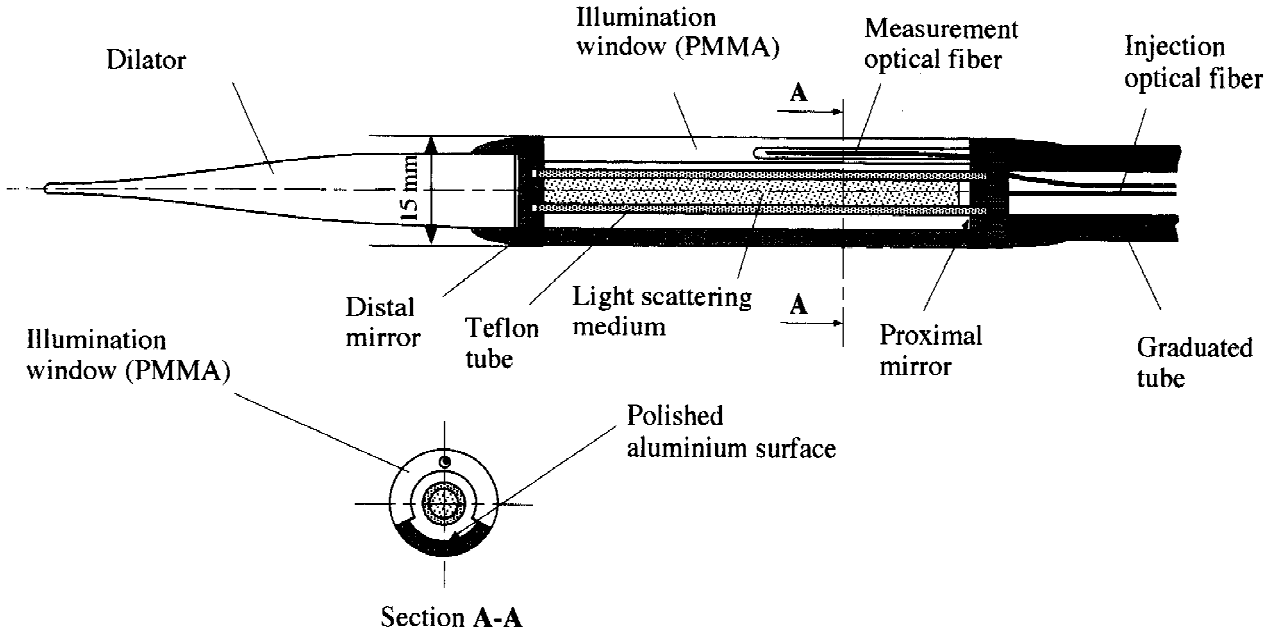

Fig. 4. Cylindrical light distributor for PDT in the esophagus. The light is guided by an optical fiber from the laser source to the esophagus light distributor. The radiant energy is then homogeneously distributed along the surface of the illumination window by using a cylinder of diffusing medium (particles of Al_2O_3 embedded in transparent silicone rubber). The homogeneity along the z axis is obtained by varying the concentration of scattering particles and the use of end mirrors. A measurement optical fibre allows to monitor the irradiance applied to the tissue and to observe the tissue fluorescence emission during the treatment. It can be used to measure the photobleaching of the dye during PDT. The dilator facilitates the insertion of the distributor into the esophagus.

nance of a residual lesion (crater), (Fig. 6c), may be observed. In order to illustrate the influence of such artifacts, it is necessary to emphasize that, e.g., a 0.2 mm displacement of the probe in the tissue results in a change of 23% of the light intensity for an effective attenuation coefficient of 1.3 mm^{-1} (a typical value in soft living tissues at 514 nm).

A second method to evaluate the radiant energy fluence rate distribution in the tissue consists of modelling light propagation in such a medium. This approach assumes the knowledge of several parameters characterizing the tissue and the light distributor. Analytical models are available to describe light propagation in stratified tissues [23], but essentially only ex vivo measurement techniques can be used to determine the individual optical properties of each tissue layer. Such ex vivo measurements again may introduce many artifacts such as the above noted postmortem changes of the tissue optical properties. The most commonly used analytical models are based on the diffusion approximation of the photon transport equation [24,25] and require, for a macroscopically homogeneous tissue, three tissue optical parameters, namely, an absorption coefficient, a reduced scattering coefficient, and a relative refractive index. These models are suitable for a highly diffusing medium. The accuracy decreases close to the tissue surface and at the proximity of a collimated light source, in particular in the case of an anisotropic scattering medium. Numerous measuring techniques are being investigated in order to determine these optical parameters [14,15,26–33] in situ. The measuring technique used in our experiments is noninvasive and is based on the spatial distribution of the diffuse reflectance at the tissue surface. We have developed several probe prototypes for clinical application [37]. The probe used in the clinical experiments described below was designed to measure the optical properties of the esophagus wall in geometrical conditions identical to those used by us in photodynamic therapy. To obtain a more accurate description of the radiant energy fluence rate in the tissue, solutions of the transport equation [34] can be used for simple experimental conditions. For more complex conditions, a simulation technique such as the Monte Carlo method [35,36] can be utilized. Such models need a more

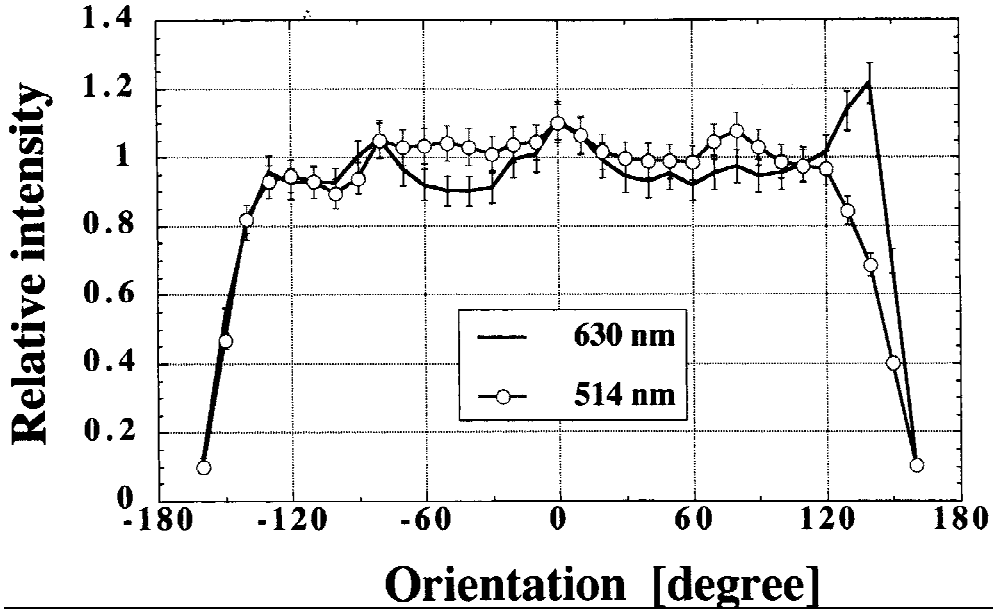

Fig. 5. Typical normalized angular response of the isotropic probe at 514 and 630 nm, measured in water. Similar isotropy is obtained in air.

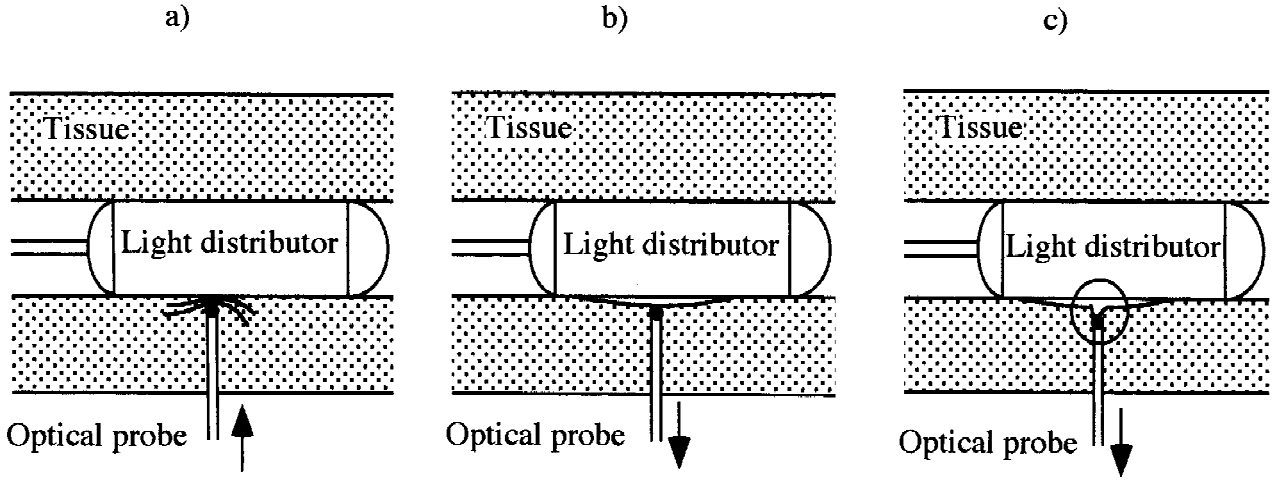

Fig. 6. Typical artifacts during radiant energy fluence rate measurement by means of an optical microprobe: (**a**) tissue compression, (**b**) tissue detachment from the light source surface, (**c**) preserving a residual probe induced lesion.

accurate description of the scattering, such as knowledge of the anisotropy parameter and possibly even the detailed shape of the scattering phase function. The anisotropy parameter is the average cosine of the scattering angle and the scattering phase function describes the angular distribution of the light intensity due to a mean scattering event. Until now, these quantities have been obtained only from ex vivo measurements.

RESULTS AND DISCUSSION

After presenting materials used to perform PDT in the esophagus and to obtain information on the light propagation in the wall of this organ, we hereafter emphasize some simple notions of dosimetry. These can be used together with an approximate knowledge of the optical properties of the tissue in order to guide clinical tests as well as to obtain a safer and more effective PDT treat-

ment, in this particular case in the esophagus. Optical properties have been measured ex vivo and in vivo with the previously described techniques for two wavelengths of interest in PDT with the presently clinically used photosensitizers.

These notions, although based on simple modelling of the photodynamic treatment, can also be of considerable help in interpreting PDT results.

Light Distribution: Model and Measurement

In the following, the radiant energy fluence rate distribution $\phi(z)$ in a "macroscopically homogeneous" tissue is described by the simple model:

$$\phi(z) = KIoe^{-\alpha z} \quad (1)$$

with Io: The irradiance measured in air at the surface of the light distributor [W/cm^2].
K: The parameter describing the radiant energy fluence rate increase in going from air into a diffusing medium.
α: The extinction factor [mm^{-1}]

This is a somewhat heuristic model in which we avoid using proper parameters given by the physical models proposed in the literature, such as the effective attenuation coefficient. It should be noted that in some cases, e.g., large surface area illumination of a semi-infinite highly diffusing medium, the so-called extinction factor α and the effective attenuation coefficient are effectively identical. The simplified model used here describes the radiant energy fluence rate distribution in numerous clinical conditions reasonably well. Thus under the experimental conditions of PDT in the esophagus, the model is especially suitable as can be seen in Figure 7. This figure shows ex vivo measurements of the radiant energy fluence rate distribution in the wall of a resected human esophagus. These measurements have been performed by using the isotropic optical microprobe [14,15] at different wavelengths of interest in PDT with Photofrin II and meso-tetrahydroxyphenylchlorin (m-THPC), namely, at 514 nm (cw Ar^+ laser), 630 nm, and 652 nm (cw Ar^+ pumped dye laser). The light distributor is the same as that used in clinical PDT and is shown in Figure 4. The experimental setup is illustrated schematically in Figure 8.

Monte Carlo simulations based on in vivo measurements of the optical properties of the

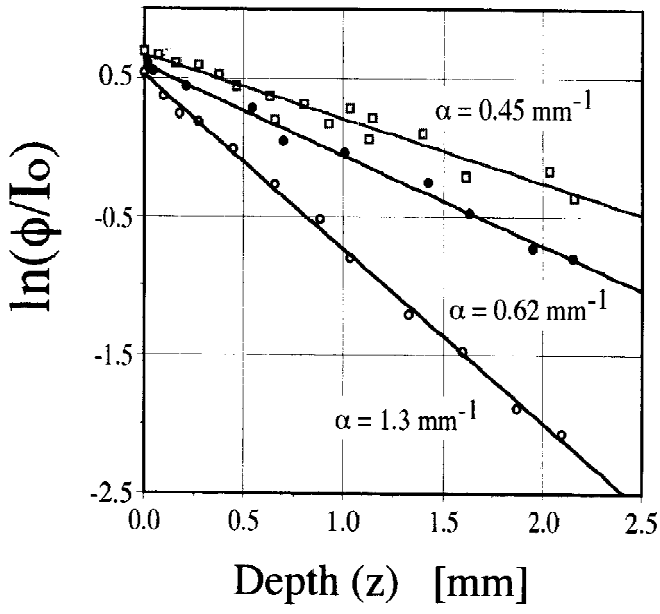

Fig. 7. Radiant energy fluence rate distribution measured in the wall of a resected human esophagus irradiated with the specially designed light distributor (see Fig. 4) for homogeneous irradiation over various lengths of the esophagus (here, 4 cm). Light intensities at 652 (□), 630 (●), and 514 (○) nm are plotted on a logarithmic scale versus the distance between the illumination light distributor surface and the probe. Io is the irradiance measured in air at the light distributor surface. The radiant energy fluence rate distribution is well described by a decreasing exponential with an extinction factor α.

esophageal wall [34] gave smaller values of the extinction factor. In particular, we obtained the following typical mean values: 0.8 mm^{-1} at 514 nm and 0.24 mm^{-1} at 630 nm. These in vivo measurements were performed on 20 patients at 514 nm and 11 patients at 630 nm with the noninvasive technique based on the spatial distribution of the diffuse reflectance at the tissue surface. The disagreement illustrates the importance of in vivo measurements. In the following, we will use these mean in vivo parameters.

Light Penetration Depth and Theoretical Necrosis Depth

In the proposed simplified model, the penetration depth of the light is defined by $\delta = 1/\alpha$ [mm] and indicates the distance from the source where the radiant energy fluence rate in the tissue is lowered by a factor of 1/e, to ~36%, of its maximum value. This distance must not be confused with the necrosis depth obtained in PDT. It is theoretically possible to cause necrosis in any tissue thickness by an appropriate PDT treatment. In reality, the light dose is limited by ther-

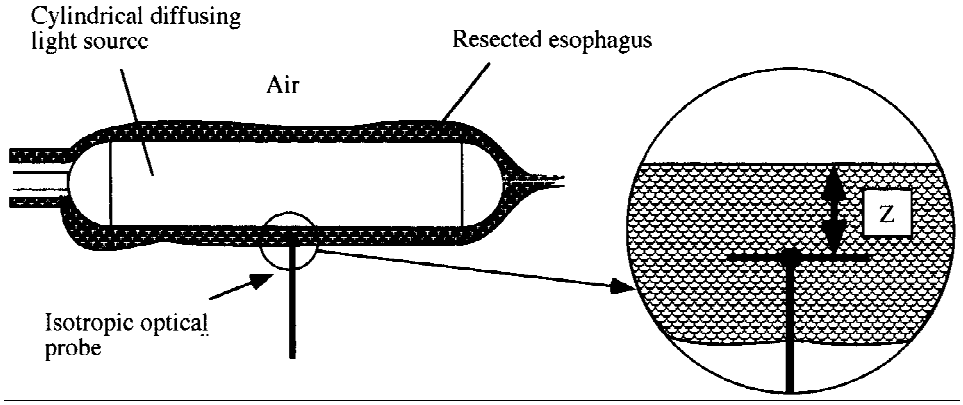

Fig. 8. Ex vivo radiant energy fluence rate measurement in the wall of the resected human esophagus: the experimental setup. The cylindrical light diffuser in this case has a diameter of 15 mm and radiates over a length of 40 mm.

mal effects (i.e., limitation on the irradiance [W/cm^2]), and on treatment duration. Moreover, it is important to emphasize that since the radiant energy fluence rate in the tissue is described by an exponential function, the necrosis depth is not a linear function of the illumination light intensity. In other words, doubling the irradiance does not correspond to doubling the necrosis depth.

To illustrate these ideas, let us consider a homogeneous tissue with a given concentration of photosensitizer. We assume that, to a first approximation, the necrosis process at any place in the tissue is related only to the photosensitizer concentration and the radiant energy density [J/cm^3] in this area. The photobleaching, i.e., the photoinduced destruction of sensitizer during the treatment, is supposed to induce only a nonproportionality between the effect of the radiant energy fluence rate and the decrease in the photosensitizer concentration. Thus we also assume that the sensitizer concentration decrease does not change the light absorption in the tissue significantly. In the current clinical context, photosensitizer absorption is negligible in comparison with the tissue absorption, especially for relatively highly phototoxic sensitizers such as m-THPC [12]. E_{thr} is defined as the minimum radiant energy density necessary for tissue to cause necrosis (i.e., the therapeutic threshold value). I_N [W/cm^2] is defined as the irradiance applied at the tissue surface to obtain a tissue necrosis depth of z_o. It is useful to evaluate the increase in the necrosis depth due to an increase of the irradiance (ΔI_N) in connection with the tissue optical properties. This variation of the necrosis depth in PDT also can be induced by a change in the tissue optical properties. It also can be affected by the variation of the photosensitizer concentration in the tissue or by varying its therapeutic effectiveness. These changes can occur as natural variations between two patients. Figure 9a shows the calculated increase of necrosis depth as a function of the extinction factor α in the case of an increase by a factor 2 of the irradiance ($\Delta I_N = I_N$).

Figure 9b shows the variation of the necrosis depth as a function of $\Delta I_N/I_N$ for the different extinction factors concerned. As we see in these graphs, the effect of the irradiance doubling is a maximal necrosis depth increase of ~0.9 mm at 514 nm and 2.9 mm at 630 nm, and this increase is independent of the value I_N. From the experimental clinical point of view, it means that if a treatment at 514 nm has not induced any necrosis with a given irradiance Io, it is possible to increase the irradiance by a factor 2 without theoretically risking an esophagus wall perforation, assuming that the other conditions are preserved. It is important to note that the esophageal wall is typically < 2 mm thick in our PDT conditions. We can also deduce from these graphs and measurements that if, e.g., a clinical treatment at 514 nm in one patient has induced a tissue necrosis depth of 0.5 mm, a safe treatment under the same illumination conditions for another patient is possible with a change by a factor 2 in the K parameter. At the other wavelength considered, the problem is quite different. At 630 nm, a mistake by a factor 2 in the light dosimetry implies significant risks of perforation. This clearly emphasizes the importance of the wavelength choice from a safety point of view if most of the present photosensitizers that have insufficient selectivity

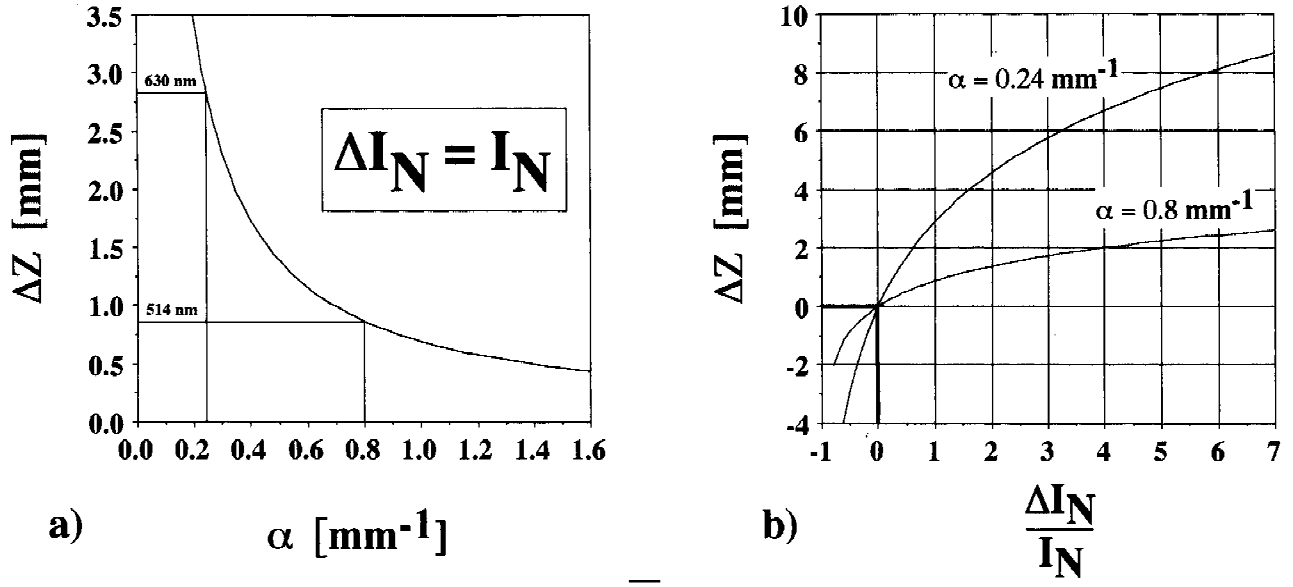

Fig. 9. (**a**) Increase of the necrosis depth caused by doubling the irradiance at the surface of a homogeneous tissue, as a function of the extinction factor α. The values of the extinction factor have been obtained by in vivo measurements in a human esophagus wall. (**b**) Variation of the necrosis depth in an homogeneous tissue as a function of the variation of the irradiance at the tissue surface for different extinction factors measured in vivo in the esophagus wall.

at the applied conditions are used. So far we assumed a precisely known extinction factor. If we consider an extinction factor uncertainty, the uncertainty in the necrosis depth can be estimated. The extinction factor uncertainty can be due to the limited accuracy in its measurement if this parameter is determined before each photodynamic treatment, or it may be due to the change of the tissue optical properties from patient to patient when the extinction factor is a mean value obtained from many previous measurements. The relative error E_z on the necrosis depth and the relative error E_α on the extinction factor are linked by the relation:

$$E_z = \frac{-E_\alpha}{1 + E_\alpha} \qquad (2)$$

For instance, if the extinction factor is overestimated by 20% ($E_\alpha = -0.2$), the necrosis depth is underestimated by 25%.

These conclusions, of course, should be considered within the realm of our simplified model.

Photosensitizer Concentration Selectivity, Therapeutic Selectivity, and Necrosis Spatial Selectivity

We once again consider a simple model in order to describe the PDT process and to offer some basic rules in the context of the light dosimetry. We consider a homogeneous tissue containing a tumor and assume a higher photosensitizer concentration in the tumor as compared to the surrounding normal tissue. This selectivity implies a difference in the minimal radiant energy density necessary for necrosis, $E_{thr(tissue)} > E_{thr(tumor)}$, assuming, for simplicity sake, that the tissue response (necrosis) is the same for the lesion and the normal tissue. Due to photobleaching, the therapeutic selectivity ratio $E_{thr(tissue)}/E_{thr(tumor)}$ is not simply the inverse of the photosensitizer concentration ratio [11]. Furthermore, assuming equal tissue optical properties in the tumor and in the healthy tissue, we can evaluate, for a given selectivity, the maximum difference of the necrosis depth between both tissues, and in particular the tumor thickness, which we are able to treat without damaging the healthy surrounding tissue (see Fig. 10). This thickness is equal to $\ln\{E_{thr(tissue)}/E_{thr(tumor)}\}/\alpha$ and is plotted in Figure 11 against the therapeutic selectivity ratio $E_{thr(tissue)}/E_{thr(tumor)}$ for wavelengths of current interest. α, in mm^{-1}, has been previously defined as the extinction factor of the radiant energy fluence rate in the tissue.

One observes that whereas the treatment at 514 nm improves the safety of PDT in the esophagus, it obviously decreases the necrosis selectiv-

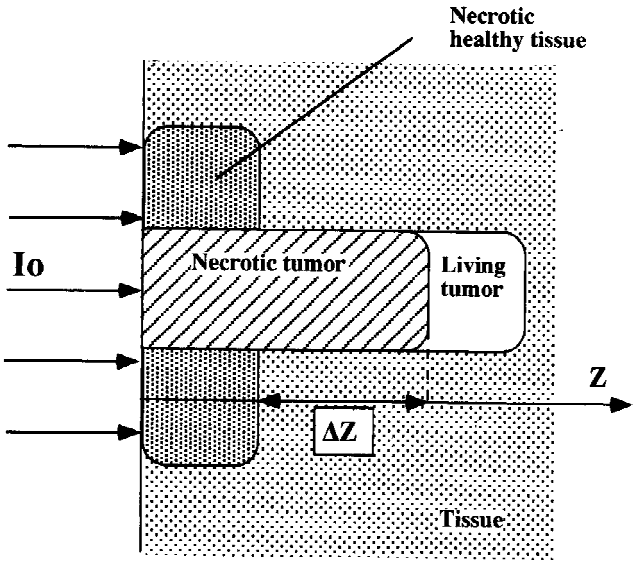

Fig. 10. Maximal difference of necrosis depth between tumor tissue and healthy surrounding tissue.

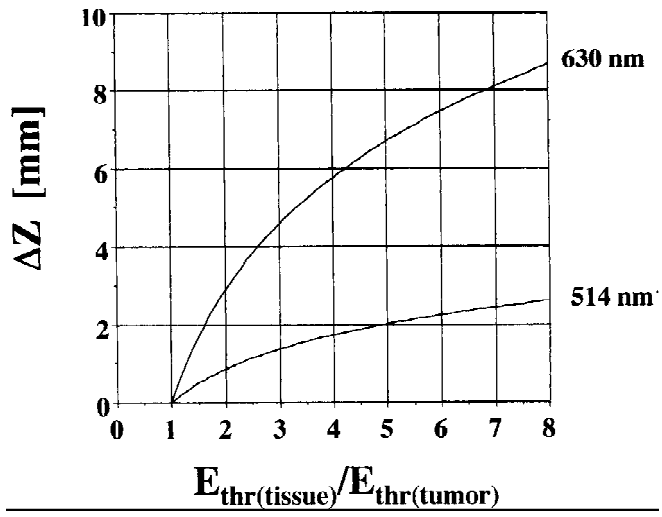

Fig. 11. Maximum difference of necrosis depth between tumor tissue and healthy surrounding tissue as a function of the therapeutic selectivity ratio $E_{thr(tissue)}/E_{thr(tumor)}$.

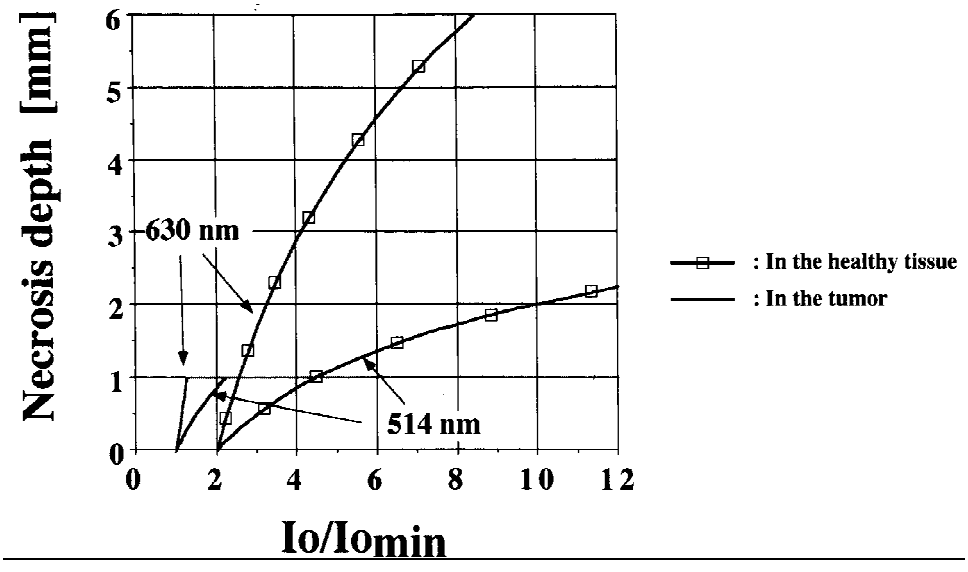

Fig. 12 Necrosis depth as a function of the normalized irradiance in a 1 mm thick tumor and in the healthy tissue of the esophagus. Io_{min} is the minimal irradiance to obtain tissue necrosis at the tumor surface. A therapeutic selectivity of 2 is considered.

ity and, therefore, may somewhat increase the risk of stenosis for a curative treatment in the case of a 360° irradiation. The graph in Figure 11 can be used in clinical experimentation to estimate, in the context of our hypothesis, the therapeutic selectivity ratio $E_{thr(tissue)}/E_{thr(tumor)}$ from the observation of biopsy or autopsy samples (i.e., from the necrosis depth Δz measurement, after treatment).

Selectivity and Risk of Perforation

In the case of early squamous cell carcinomas in the esophagus, the most serious medical complication we have encountered in PDT is wall perforation (fistula). Let us consider a tumor of known thickness (i.e., in the order of 1 mm in our medical application). If we assume that the irradiance I_N has been evaluated theoretically or ex-

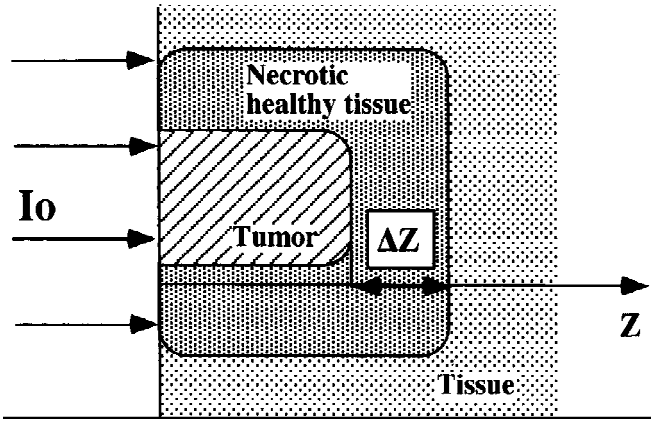

Fig. 13. Healthy tissue thickness necrosed beyond the tumor.

perimentally, it is, therefore, useful to determine the risk of perforation induced by an error in this estimation. Such an error may be due, e.g., to an inaccurate knowledge of the optical properties of the tissue, or to an underestimation of the photosensitizer concentration or phototoxic effectiveness.

Figure 12 shows the increase of the necrosis depth in the tumor and in the healthy tissue of the esophagus as a function the irradiance increase. We consider a therapeutic selectivity of 2 and a tumor thickness of 1 mm. As it appears from this graph and from Figure 11, it is not possible in these conditions to eradicate the whole tumor with a 514 nm illumination without damaging the surrounding healthy tissue to some extent. On the contrary, an illumination at 630 nm allows us to define an ideal irradiance from this point of view, that means without considering the risk of esophageal wall perforation.

We now calculate for different therapeutic selectivity ratios the healthy tissue thickness necrosed beyond the tumor as a function of the dosimetry error (see Figs. 13, 14). When the ratio R between Io_{estim}, the estimated irradiance actually used for the PDT, and Io_N, the minimal irradiance suitable to treat all the tumor but not the underlying normal tissue, is equal to the therapeutic selectivity ratio, the necrotic tissue thickness is identical in the tumoral tissue and in the surrounding healthy tissue. For a higher dosimetry error, necrosis of healthy tissue beyond the tumor can occur with risk of perforation. For instance, in the case of an 0.5 mm thick tumor and a therapeutic selectivity ratio of only 2, the optimal irradiance can be multiplied by at most a factor of 5 at 514 nm without perforation of the esophagus wall being induced.

CONCLUSIONS

Photodynamic therapy has been shown to be an effective treatment for the cure of superfiial cancers in the pharynx, esophagus, and tracheo-

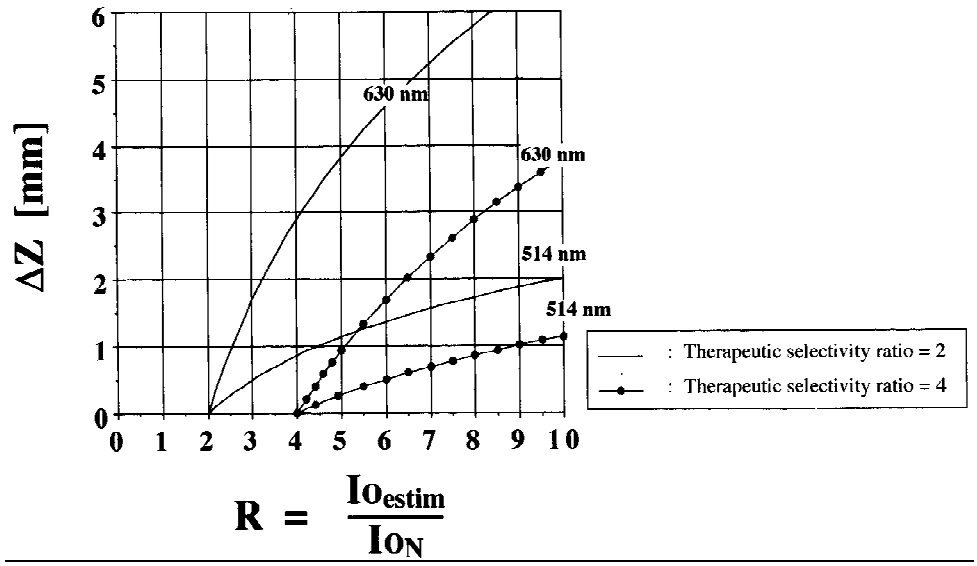

Fig. 14. Necrosis depth in the healthy tissue beyond the tumor due to an inaccurate light dosimetry. Io_{estim} is the estimated irradiance applied to the tissue surface. Io_N is the irradiance suitable for obtaining the eradication of the tumor without necrosing the underlying healthy tissue.

bronchial tree. However, the lack of selectivity of some of the current clinically used photosensitizers implies a risk of fistula, i.e., perforation of the wall of the treated organ in some cases, in particular in the esophagus. Consequently, special care with the optical dosimetry is required, i.e., the control of the spatial distribution of the light in the treated tissue is essential.

Here, we have considered a relatively simple model to describe this distribution. The model used is, however, suited to numerous experimental conditions, especially to those we obtain during a photodynamic treatment in the esophagus with the endoscopic light source we developed for this purpose. We have shown the consequences of such a light distribution on the necrosis depth and on the selectivity of the treatment. These simple notions of dosimetry have been associated with some experimental values of tissue optical properties obtained ex vivo and in vivo in the esophagus wall for several wavelengths of interest in PDT. They allow in a clinical experimental approach, such as the study of a new photosensitizer, to obtain, as fast as possible, a safe and efficient treatment. Treatment at a wavelength with low penetration depth (i.e., green light) allows a reduction in the risk of fistula. This improvement, however, is unfortunately obtained together with the inherent loss of necrosis selectivity, i.e., increased risk of superficial photodynamic damage to the surrounding normal tissue.

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